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Guarding against nonmelanoma skin cancer in solid organ transplant recipients

Periodic skin examination and ongoing counseling are central in your posttransplantation care of these patients at high risk of skin malignancy.

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PRACTICE RECOMMENDATIONS

› *Conduct a full-body skin examination at least once annually for solid organ transplant recipients.* (C)

› *Encourage daily use of broad-spectrum SPF ≥ 30 sunscreen and sun-protective clothing (long sleeves, pants, wide-brimmed hats) for these patients.* (A)

› *Consider chemoprophylactic agents for patients at especially high risk of nonmelanoma skin cancer.* (A)

› *Treat nonmelanoma skin cancer in a solid organ transplant recipient aggressively because of their increased risk of recurrence, local invasion, and metastasis.* (B)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence

(B) Inconsistent or limited-quality patient-oriented evidence

(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

The incidence of posttransplant malignancy among solid organ transplant recipients (SOTRs) is 10%; skin cancer, primarily nonmelanoma skin cancer (NMSC), constitutes 49.5% of all malignancies in this population.[1] The etiology of the increased risk of cutaneous malignancy in SOTR is multifactorial:

- The skin of SOTRs is photosensitive, compared to that of immunocompetent patients, thus predisposing SOTRs to carcinogenic damage resulting from exposure to UV light.[2]
- Immunosuppression plays a key role in increasing the risk of cutaneous malignancy by inhibiting the ability of the immune system to recognize and destroy tumor cells.[3]
- Human papillomavirus (HPV) can play a role in carcinogenesis by promoting molecular pathways to proliferation and survival of nascent tumor cells[4]; β-HPV strains are disseminated ubiquitously in the skin of immunosuppressed patients.[5]
- Some medications administered after transplantation can be directly carcinogenic.

NMSC in SOTRs also differs qualitatively from NMSC in immunocompetent patients. Cutaneous squamous cell carcinoma (cSCC) (**FIGURES 1** and **2**) is the most common skin cancer among SOTRs, whereas basal cell carcinoma (BCC) is the most common skin cancer in the general population.[3] cSCC in the SOTR population tends to be more aggressive, with more rapid local invasion and an increased rate of both in-transit and distant metastases, leading to an increase in morbidity and mortality. Mortality of metastatic cSCC among SOTRs is approximately 50%, compared to 20% in an otherwise healthy population.[3,6-8]

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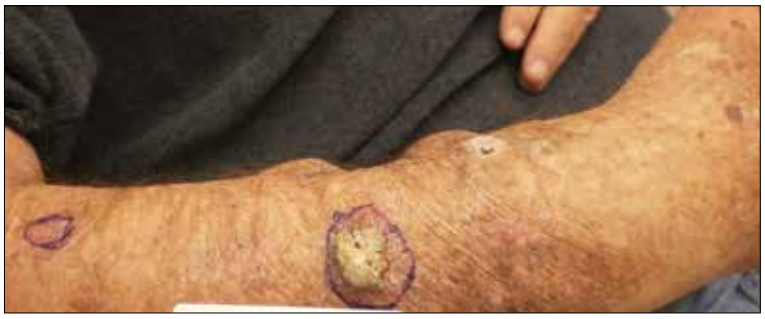
FIGURE 1

Cutaneous squamous cell carcinoma in a renal transplant recipient

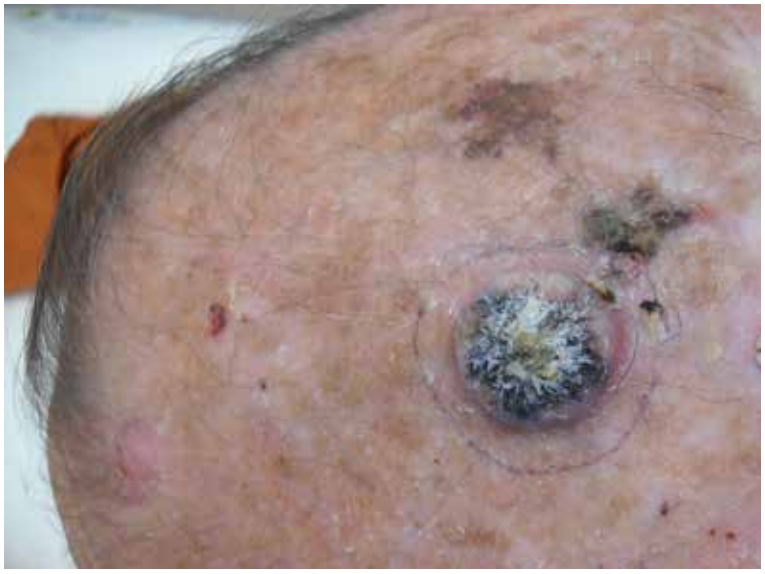


PHOTOS COURTESY OF THOMAS STASKO, MD

Hyperkeratotic plaque, with surrounding erythema, is seen on the patient's right arm.

FIGURE 2

Squamous cell carcinoma, diffuse actinic damage on solid organ transplant patient's scalp



Hyperkeratotic, dome-shaped nodule is seen on the patient's scalp.

The problem is relevant to primary care

Screening. Because there is a demonstrated reduction in morbidity and mortality associated with early detection and treatment of NMSC, regular screening of skin is important in the SOTR population.[9] A study in Ontario, Canada, from 1994 to 2012 and comprising 10,183 SOTRs, found that adherence to an annual skin check regimen for ≥ 75% of the observation period was associated with a 34% reduction in cutaneous BCC- and cSCC-related morbidity or death (adjusted hazard ratio = 0.66; 95% CI, 0.48-0.92).[10] Although routine follow-up with a dermatologist is recommended for SOTRs,[9,11-15] only 2.1% of patients in the Canadian study were fully adherent with annual skin examination, and 55% never visited a dermatologist.[10] Consequently, primary care physicians can play a key role in skin cancer screening for SOTRs.

Education regarding the importance of protection from the sun is also an essential part of primary care. A 2018 study of SOTRs in Turkey demonstrated that[16]

- 46% expressed a lack of knowledge of the hazards of sun exposure
- 44% did not recall ever receiving medical advice regarding sun protection
- 89% did not wear sun-protective clothing
- 86% did not use sunscreen daily.

Multiple studies have demonstrated the positive effect that preventive education and attendance at a dermatology or skin cancer screening clinic can have on sun-protective behaviors among SOTRs.[9,16-18] In the Turkish study, 100% of patients who reported using sunscreen daily had been undergoing regular dermatologic examination.[16]

In this article, we review current management guidelines regarding the prevention and treatment of NMSC in SOTRs.

Recommendations for prevention

Screening skin exams (TABLE 1[1,11,12,15,19-23]). Although definitive guidelines do not exist regarding the frequency of a screening skin exam for SOTRs, multiple frequency-determining algorithms have been proposed.[11,12,15,19] The recommended frequency of a skin exam is based on history of skin cancer; for SOTRs, the most common recommendation[19] is a full-body skin examination as follows:

- *annually*—when there is no history of skin cancer
- *every 6 months*—when there is a history of actinic keratoses (AKs; precancerous lesions that carry a risk of transforming into cSCC) or a single low-risk NMSC

TABLE 1

Skin cancer screening and sun-protective recommendations for solid organ transplant recipients[1,11,12,15,19-23]

Topic (SORT grade)	Recommendations
Details of the screening appointment (**A**) [1,11,12,15,19-22]	Review immunosuppressive regimen
	Perform full-body skin exam • Biopsy all suspicious lesions • Palpate draining lymph nodes when there is a history of NMSC • Treat actinic keratoses with liquid nitrogen or field therapy
	Evaluate sun-protective habits • Current habits • Knowledge of recommended habits • Knowledge of risks associated with nonadherence
Frequency of screening appointment (**C**) [11,12,15,19]	• No history of skin cancer: 12 mo • History of actinic keratoses or a single low-risk NMSC: 6 mo • History of multiple NMSCs or a single high-risk NMSC: 3 mo • History of metastatic NMSC: 1-3 mo
Sun-protection recommendations (**A**) [15,23]	Use sunscreen daily • Broad-spectrum product • SPF ≥ 30 • Reapply after 2 h of sun exposure, in accordance with labeling Wear sun-protective clothing (long sleeves, pants, hat, sunglasses) Avoid patronizing tanning salons

NMSC, nonmelanoma skin cancer; SORT, Strength of Recommendation Taxonomy.

- *every 3 months*—when there is a history of multiple NMSCs or a single high-risk NMSC
- *every 1 to 3 months*—when there is a history of metastatic disease.

Other risk factors for NMSC to consider in SOTRs when determining an appropriate follow-up regimen include any of the following[1,20,21,24-26]:

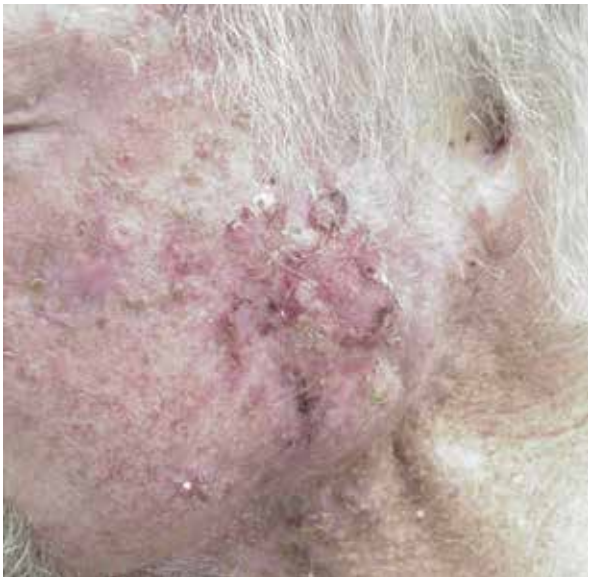
- male gender, fair skin, history of childhood sunburn, history of smoking
- lung or heart transplantation, history of episodes of transplant rejection, age ≥ 50 years at transplantation
- immunosuppression with calcineurin inhibitors, compared to mammalian target of rapamycin (mTOR) inhibitors
- immunosuppression with cyclosporine, compared to tacrolimus
- an immunosuppressive regimen with > 1 immunosuppressant or an increased degree of immunosuppression
- antithymocyte globulin within the first year posttransplantation.

Because the intensity of immunosuppression and individual immunosuppressants used affect the risk of NMSC, conduct a thorough medication review with SOTRs at all visits. Ask about new, changing, or symptomatic (pruritic, painful, bleeding) skin lesions, and perform a full-body skin exam. Palpate draining lymph nodes if the patient has a history of NMSC.[15] AKs (**FIGURE 3**) should be treated aggressively with liquid nitrogen or field therapy. Lesions suspicious for NMSC should be biopsied and sent for histologic evaluation.[22] Shave, punch, and excisional biopsies are all adequate techniques; however, because all cSCCs in SOTRs are considered high risk for aggressive features, biopsy should extend at

Regular screening of skin is important in the solid organ transplant population.

FIGURE 3

Multiple actinic keratoses on the left cheek of a renal transplant patient



Numerous hyperkeratotic papules, with adherent scale and underlying erythema, are seen on this patient. The color variation and multiple telangiectasias on surrounding skin represent chronic sun damage.

least into the reticular dermis to allow evaluation for invasive disease.[22]

Sun-protective measures (TABLE 1[1,11,12,15,19-23]). Inquire about patients' habits related to protection from the sun, their knowledge of recommended sun-protective measures, and risks associated with nonadherence. Recommended sun-protective measures include

- daily broad-spectrum sunscreen (SPF ≥ 30), reapplied every 2 hours of sun exposure, in accordance with labeling instructions[23]
- sun-protective clothing (pants, long sleeves, hat, sunglasses)[23]
- avoidance of tanning salons.[15]

SOTRs who adequately adhere to sun-protective measures might need vitamin D supplementation because sunscreen and sun-protective clothing inhibit cutaneous synthesis of vitamin D.[15]

Recommendations for treatment

Consider chemoprophylactic therapy for SOTRs who have had multiple prior cutaneous malignancies or multiple AKs.

Topical chemoprophylaxis

Topical medications used for cSCC chemoprophylaxis include 5-fluorouracil (5-FU), photodynamic therapy (PDT), imiquimod, ingenol mebutate, topical retinoids, and diclofenac.[27] (See TABLE 2.[27-40]) Of these, the latter 3 are used less commonly because of the small packaging size of ingenol mebutate and the relative lack of efficacy data for topical retinoids and diclofenac.[27] Imiquimod is often avoided when treating large surface areas because of the risk of systemic adverse effects associated with cytokine release.[27]

5-FU is US Food and Drug Administration (FDA)-approved for the treatment of AKs, and is used off-label for treating cSCC in situ (Bowen disease). It is the most commonly used topical therapy for field disease.[27-29] 5-FU is typically applied once or twice daily for 3 to 4 weeks. Common adverse effects include transient skin irritation and erythema.[27]

PDT involves topical application of a photosensitizer, such as 5-aminolevulinic acid or methyl aminolevulinate, followed by exposure to a visible light source, leading to antitumor effects on gene expression and destruction of proliferating cells through production of reactive oxygen species.[30,31] Evidence is sufficient to support routine use of PDT for AKs and Bowen disease.[30] A mild sunburn-like reaction is common following PDT, with transient erythema and discomfort typically lasting 1 to 2 weeks but not typically necessitating analgesic therapy.[27]

Imiquimod is a ligand that binds to and activates Toll-like receptor 7, leading to enhancement of the cell-mediated antitumor immune response and resultant tissue-specific apoptosis coordinated by type 1 T-helper lymphocytes.[32] Topical imiquimod cream is FDA approved for field treatment of AKs at 2.5%, 3.75%, and 5% concentrations; efficacy has been demonstrated in the SOTR population.[33,41] Multiple studies in immunocompetent patients have suggested that imiquimod might be slightly less efficacious than 5-FU.[42-44]

The tolerability of field treatment with imiquimod has been called into question.[27]

TABLE 2

Chemoprophylaxis options[27-40]

Drug or therapy (SORT grade)	Indication	Dosing	Mechanism	Adverse effects	Notes
5-Fluorouracil **(A)**[27-29]	Field therapy of multiple actinic keratoses	0.5% cream, applied qd, for ≤ 4 wk 5% cream, applied bid, for 2-4 wk	Cytotoxic pyrimidine analogue; induces cell-cycle arrest and apoptosis	Transient skin irritation and erythema	
Photodynamic therapy **(A)**[27,30,31]		Topical application of photosensitizer, followed by exposure to visible light source Optional repeat treatment, 1-4 wk later	Antitumor effects on gene expression and destruction of proliferating cells through production of reactive oxygen species	Transient skin irritation and erythema, less commonly blistering and desquamation	Sun-protective measures advised for ≥ 48 h following photodynamic therapy to mitigate severity of skin irritation
Imiquimod **(B)**[27,32,33]		2.5% or 3.75% cream applied nightly during two 14-d treatment cycles separated by a 14-d rest period 5% cream, applied at bedtime twice a wk for 4 wk	Activation of Toll-like receptors, resulting in enhancement of cell-mediated immunity and tissue-specific apoptosis via type 1 T-helper lymphocytes	Transient skin irritation and erythema, less commonly skin erosion or ulceration May lead to significant systemic adverse effects associated with cytokine release when applied to large surface areas	
Diclofenac **(B)**[27,34]		3% gel applied bid for 60-90 d	Decreases prostaglandin production by reversibly inhibiting cyclooxygenase-1 and cyclooxygenase-2	Transient skin irritation Less commonly, desquamation, elevated liver function tests, flu-like symptoms, headache, paresthesias	
Nicotinamide **(B)**[27,35,36]	Systemic cSCC chemoprophylaxis (eg, multiple prior cutaneous malignancies)	500 mg orally bid	Supports repair of DNA damage resulting from ionizing radiation (ie, ultraviolet light)	Flushing, hepatotoxicity (at dosages > 3 g/d)	Efficacy data are limited in the transplant population; long-term antitumor efficacy is unknown Do not substitute nicotinic acid or niacin for nicotinamide, because of their associated increased incidence of flushing

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However, in a 2019 study comparing adverse reactions among 513 immunocompetent patients with field disease who were treated with either 5-FU 5% cream; imiquimod 5% cream; PDT with methyl aminolevulinate; or ingenol mebutate 0.015% gel, a similar or smaller percentage of patients treated with imiquimod reported moderate-to-severe itching, moderate-to-severe pain, and any adverse events, compared to patients treated with the other options.[44]

Diclofenac is a nonsteroidal anti-inflammatory drug that reversibly inhibits the enzymes cyclooxygenase-1 and

TABLE 2

Chemoprophylaxis options[27-40] (*cont'd*)

Drug or therapy (SORT grade)	Indication	Dosing	Mechanism	Adverse effects	Notes
Oral retinoids[a] **(A)**[27,37,38]	Systemic cSCC chemoprophylaxis (eg, multiple prior cutaneous malignancies)	10-30 mg orally qd	Vitamin A analogue Chemoprophylactic mechanism not well understood	Teratogenicity (should generally be avoided in patients of childbearing potential), skin dryness, elevation of transaminases and triglycerides	Rebound effect (ie, treatment discontinuation leads to rapid return to baseline cSCC formation)
Capecitabine **(B)**[27,39,40]	Systemic cSCC (eg, multiple prior cutaneous malignancies)	950 mg/m^2 administered orally on Days 1-14 of a 21-d cycle, along with subcutaneous interferon alfa 3 times per wk	Prodrug metabolized to 5-fluorouracil	Increased anticoagulant effects of warfarin, fatigue, palmar-plantar erythrodysesthesia, diarrhea, neutropenia (rare), severe toxicity in patients with dihydropyrimidine dehydrogenase deficiency (rare)	Typically initiated with the help of Medical Oncology

cSCC, cutaneous squamous cell carcinoma; SORT, Strength of Recommendation Taxonomy.
[a] Acitretin.

cyclooxygenase-2, resulting in a decrease in the formation of inflammatory prostaglandins, which have been observed in chronically sun-damaged skin, AKs, and cSCC.[34,45] Diclofenac 3% gel, applied topically twice daily for 60 to 90 days has been approved by the FDA for treatment of AKs, in conjunction with sun avoidance.[34]

Topical diclofenac has been demonstrated to be efficacious in treating AKs in the SOTR population[46,47]; however, multiple meta-analyses using data from immunocompetent patients have demonstrated that topical diclofenac is inferior to other treatment options, particularly 5-FU, at achieving complete clearance of AKs.[43,48,49] Diclofenac might be a useful option when patient adherence is expected to be difficult because of adverse effects of therapy: Multiple studies have suggested that diclofenac might be more tolerable than other options.[43,48,50]

Systemic chemoprophylaxis

Systemic therapies that have been used for chemoprophylaxis against cutaneous malignancy include nicotinamide, oral retinoids, capecitabine, and HPV vaccination. (See **TABLE 2**.[27-40])

Nicotinamide, the amide form of vitamin B_3, protects against cutaneous malignancy by aiding repair of DNA damaged by ionizing radiation, such as UV light.[27] Efficacy has been demonstrated in reducing development of new AKs and cSCC in immunocompetent patients with a history of more than 2 keratinocyte carcinomas within a 5-year span.[27,35] Nicotinamide is especially relevant to the SOTR population because it reduces the level of cutaneous immunity suppression induced by UV radiation without altering patients' baseline immunity.[27,36]

There are insufficient long-term follow-up data in the literature to assess the sustainability of the antitumor effects of nicotinamide; studies specific to the SOTR population have been underpowered for assessing its impact on formation of cSCC.[27,35] Patients taking nicotinamide should be informed of the risk of liver failure at dosages > 3 g/d (antitumor efficacy has been demonstrated at 500 mg twice daily) and advised to avoid purchasing over-the-counter nicotinic acid or niacin as a substitute for nicotinamide, because of the increased incidence of flushing associated with their use.[27]

Oral retinoids. Systemic retinoids—in particular, acitretin—are efficacious in reducing the risk of cSCC in SOTRs.[27,37,38] The primary drawback to cSCC prophylaxis with oral retinoids is a rebound effect, in which treatment discontinuation leads to a rapid return to baseline cSCC formation.[27]

Pregnancy must be avoided while taking an oral retinoid. Because acitretin can persist in the body for years after discontinuation, its use should generally be avoided in patients of childbearing potential. An FDA black box warning states that patients of childbearing potential must be counseled to use 2 forms of birth control to avoid pregnancy for ≥ 3 years after cessation of oral acitretin. Prior to initiation of oral retinoid therapy, the following baseline laboratory tests should be obtained: complete blood count, creatinine, lipid panel, and liver function tests. For patients with a history of chronic kidney disease or renal transplantation, the lipid panel, liver function tests, and creatinine assay should be repeated with each dosage adjustment and every 3 months once goal-dosing is achieved.[27]

Capecitabine is typically initiated with the help of Medical Oncology.[27,40] A prodrug metabolized by dihydropyrimidine dehydrogenase to 5-FU, capecitabine interacts with warfarin, leading to a significant increase in prothrombin time.[39] Other adverse effects associated with oral capecitabine include fatigue, palmar-plantar erythrodysesthesia, diarrhea, and, rarely, neutropenia. Although dihydropyrimidine dehydrogenase deficiency is rare, treatment with capecitabine in patients who have this enzyme deficiency might lead to severe toxicity or death.[27]

HPV vaccination. HPV might play a role in the development of cutaneous malignancy, especially in immunosuppressed patients.[4,5] The utility of HPV vaccination in the prevention of NMSC has yet to be determined, but vaccination has been shown, in case reports, to be helpful in immunocompetent patients.[51,52] The immunogenicity of HPV vaccination in the SOTR population is uncertain, and the most common HPV types found in SOTRs are not specifically covered by available HPV vaccines.[19]

The role of immunosuppression reduction and immunosuppressive replacement

Both the degree of immunosuppression and the individual agents used can affect a patient's risk of NMSC. Immunosuppression reduction should be considered if skin cancer poses a major risk to the patient's health and if that risk outweighs the risk of graft rejection associated with immunosuppression reduction.[27] In a cohort of 180 kidney and liver SOTRs who developed de novo carcinoma (excluding NMSC) after transplantation, neither reduction of immunosuppression nor introduction of an mTOR inhibitor affected graft survival or oncologic treatment tolerance.[53] Because mTOR inhibitors have a protective effect against development of NMSC, they are the preferred choice of immunosuppressive agent from a dermatologic perspective.[1,27,54-57] Decisions regarding changes in immunosuppression are generally made by, or in collaboration with, the patient's transplant physician.

Recommendations: Treating cSCC

Risk should guide strategy

Small lesions of the trunk and extremities *without* high-risk features can be treated with a destructive method (eg, electrodessication and curettage). However, lesions of the head and neck and those found to have features consistent with an increased risk of recurrence or metastasis should be treated aggressively.[3,58,59]

Risk factors for invasive growth, recurrence, or metastasis of cSCC in SOTRs are multiple lesions or satellite lesions, indistinct clinical borders, rapid growth, ulceration, and recurrence after treatment.[60] The risk of invasive growth, recurrence, and metastasis of cSCC also increases with size and location of the lesion, according to this framework[60]:

- *any size* in scar tissue, areas of chronic inflammation, and fields of prior radiation therapy
- ≥ *0.6 cm* on hands, feet, genitalia, and mask areas of the face (central face, eyelids, eyebrows, nose, lips, chin, mandible, and temporal, preauricular, postauricular, and periorbital areas)
- > *1 cm* on cheeks, forehead, neck, and scalp
- > *2 cm* on the trunk and extremities.

In addition, specific findings on histologic analysis portend increased risk of invasive growth, recurrence, or metastasis:

- poor differentiation
- deep extension of the tumor into subcutaneous fat

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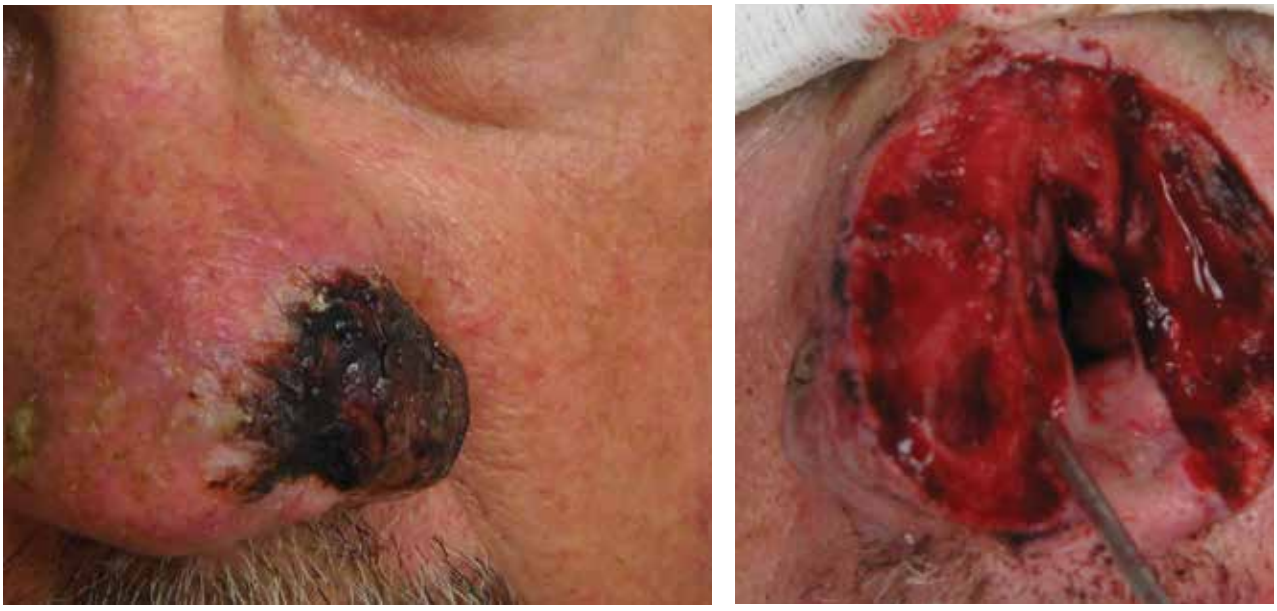
Because the intensity of immunosuppression and the individual immunosuppressants used affect the risk of nonmelanoma skin cancer, conduct a thorough medication review at all visits.

FIGURE 4

Squamous cell carcinoma treated with Mohs surgery



Left: Presurgical view. **Right**: View of the left nare after completion of Mohs surgery, but before repair of the surgical defect.

TABLE 3

Treatment of nonmelanoma skin cancer[3,7,58-61]

Malignancy	Subtype	Recommendations[a]
cSCC	Lesions without high-risk features (eg, < 2 cm on trunk or extremities)	Excision with a 4- or 5-mm margin *or* Destructive modalities (eg, ED&C)
	Lesions with high-risk features (eg, on head or neck)	*1st line* Mohs surgery (ensures margin clearance while preserving noninvolved tissue) *2nd line* Excision with postoperative margin assessment *3rd line* Systemic chemotherapy and/or radiotherapy (typically reserved for inoperable tumors or metastatic disease)
BCC	Lesions without high-risk features (eg, < 2 cm on trunk or extremities)	Excision with a 4- or 5-mm margin *or* Destructive modalities (eg, ED&C)
	Lesions with high-risk features (eg, on the central face)	*1st line* Mohs surgery (ensures margin clearance while preserving noninvolved tissue) *2nd line* Excision with postoperative margin assessment *3rd line* Systemic chemotherapy or radiotherapy (reserved for patients with high-risk BCC who are unable to tolerate surgery)

BCC, basal cell carcinoma; cSCC, cutaneous squamous cell carcinoma; ED&C, electrodessication and curettage.

[a] All recommendations in **TABLE 3** are Strength of Recommendation Taxonomy grade **B**.

- perineural invasion or inflammation
- perivascular or intravascular invasion.

Treatment modalities

Mohs surgery is preferred to ensure margin clearance while preserving noninvolved tissue[3,7] (**FIGURE 4**). If Mohs surgery is not possible, the lesion should be excised with 3- to 10-mm margins.[3,60] Based on current literature, the roles of nodal staging, sentinel lymph node biopsy, and adjuvant therapy are not well defined, but it is likely that these interventions will play a pivotal role in the management of advanced cSCC in SOTRs in the future.[3]

Nonsurgical therapeutic options for primary or adjuvant treatment of cSCC include systemic chemotherapy, radiotherapy, and programmed cell death protein 1 inhibitors. (For more on treatment modalities, see **TABLE 3**.[3,7,58-61])

Recommendations: Treating BCC

BCC in SOTRs is treated similarly (**TABLE 3**[3,7,58-61]) to how it is treated in the immunocompetent population—except that SOTRs require closer follow-up than nontransplant patients because they are at higher risk of recurrence and new NMSCs.[3] Standard management after biopsy is either[3,61]:

- Mohs surgery to ensure margin control (for most BCCs on the head and neck and those with clinical or histologic risk factors for recurrence or aggressive behavior)
- excision with a 4- or 5-mm margin or a destructive modality (for BCCs on the trunk and extremities without risk factors for recurrence).

Radiotherapy is an alternative for patients with high-risk BCCs who are unable to tolerate surgery.[3] JFP

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Consider chemoprophylactic therapy for solid organ transplant recipients who have had multiple prior cutaneous malignancies or multiple AKs.

Pregnancy must be avoided while taking an oral retinoid; because of its persistence, acitretin should generally be avoided in patients of childbearing potential.

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